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Hybrid immunity and host factors: implications on serostatus induced by COVID-19 vaccines

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Abstract

Introduction: Monitoring the humoral immune response following SARS-CoV-2 vaccination is crucial to understanding long-term protection, especially in the context of hybrid immunity (HI). This study aimed to evaluate anti-S IgG antibody levels in adults with and without prior COVID-19 infection and explore associated host-related factors. **Methods**: A cross-sectional study was conducted in 102 adults from Colombia, grouped by infection history: Group A (with prior COVID-19) and Group B (without prior COVID-19). Anti-S IgG levels were quantified using chemiluminescent immunoassay. Sociodemographic, clinical, and vaccination data were collected via survey. Statistical comparisons were performed using t-tests, Mann–Whitney U tests, and linear regression analysis. **Results**: All participants exhibited seropositivity (100%) for anti-S IgG, with high titers persisting up to 23 months post-booster. No significant differences in antibody concentrations were found between groups ($p = 0.830$). Variables such as sex, age, comorbidities, and type of vaccine did not significantly influence antibody levels. A moderate, significant correlation was found between the number of booster doses and antibody titers in Group A ($\rho = 0.453$; $p = 0.001$), but not in Group B. Regression analysis predicted progressively higher titers with additional booster doses. **Conclusions**: Robust humoral responses were observed regardless of prior infection, indicating effective vaccine-induced immunity in this population. The number of booster doses was a key factor associated with higher antibody titers, particularly in individuals with hybrid immunity. These findings support the value of continued booster campaigns and underline the need for further research into functional immunity.

Key word: hybrid immunity; SARS-CoV-2: anti-S IgG antibodies; COVID-19 vaccines; humoral immune response.

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Introduction

Hybrid immunity (HI) is defined as the robust immune response developed by vaccinated individuals who have previously experienced natural infection (1). In the context of SARS-CoV-2/COVID-19 infection, a significant increase in antibody production (25X–100X) has been demonstrated, along with broader cross-protection against viral variants and a prolonged serological status, when compared to vaccinated individuals without prior infection (2).

The World Health Organization (WHO) acknowledges and supports the concept of HI. However, public health policies have not yet been developed to incorporate the immunological benefits it offers (3). It is argued that HI remains under investigation, and its effectiveness compared to immunity acquired through natural infection or vaccination alone is not yet fully understood. Numerous variables may influence the effectiveness of HI, particularly host-dependent factors, the number of vaccine doses received, the interval between doses, and the immunization strategy (homologous vs. heterologous), among other conditions (4).

The objective of our study is to analyze the influence of HI and host-related factors on the baseline concentration of IgG antibodies against the SARS-CoV-2 Spike protein in a city on the Colombian Caribbean coast. This constitutes an analysis of serological status in a post-pandemic context.

Methods

Study Design

An analytical, cross-sectional observational study was conducted to assess baseline anti-Spike IgG antibody concentrations in adults vaccinated against COVID-19, with or without prior SARS-CoV-2 infection.

Population and Sample

The study included 102 participants aged 18 years or

older, of both sexes, enrolled in the Colombian National COVID-19 Immunization Program and residing in Barranquilla, Colombia. A simple random sampling method was used. The sample size was calculated using the formula for finite populations, considering the following parameters: a standard deviation (σ) of 0.5, a 95% confidence level ($Z = 1.96$), and a 5% margin of error ($\varepsilon = 0.05$), yielding a final sample size of 102 individuals.

- Group A (Hybrid Immunity): 51 participants with a confirmed history of SARS-CoV-2 infection and subsequent COVID-19 vaccination. Prior infection was confirmed by molecular and/or serological testing.
- Group B (Vaccine-Induced Immunity only): 51 participants with no known history of SARS-CoV-2 infection and who had been vaccinated against COVID-19. All were asymptomatic for at least one month prior to vaccination.

Recruitment was carried out between March and June 2024 according to inclusion, exclusion, and elimination criteria.

Data Collection

A structured questionnaire was administered to collect sociodemographic, anthropometric, and clinical data, including comorbidities, habits, and COVID-19-related medical history.

Laboratory Procedures

Venous blood samples were collected from each participant following informed consent and verification of eligibility criteria. Plasma was obtained and handled in accordance with standard biosafety protocols. Samples were processed and stored at the Molecular Biology and Immunology Laboratory of Universidad Libre, Barranquilla campus.

Quantification of anti-Spike IgG antibodies was performed using the commercial LIAISON® SARS-CoV-2 TrimericS IgG assay (CLIA) (Manufacturer: LIAISON, REF: P/N311510, 110-test kit). The assay targets full-length trimeric Spike protein of SARS-CoV-2, mimicking its native conformation. Results were reported as positive or negative and included semiquantitative values ranging from 13 to 2080 Binding Antibody Units per milliliter (BAU/mL), according to manufacturer specifications.

Statistical Analysis

Data were entered into a Microsoft Excel database and analyzed using IBM SPSS Statistics® version 20. Descriptive statistics were expressed as means and standard deviations for continuous variables and as proportions for categorical variables.

Normality was tested using the Shapiro–Wilk test (for $n<50$) or the Kolmogorov–Smirnov test (for $n\geq50$). Levene's test was applied to evaluate homoscedasticity (equal variances). A two-sided α level of 0.05 was used for statistical significance.

For comparisons between two groups, Student's t-test was used when assumptions of normality and equal variances were met; otherwise, the Mann–Whitney U test was applied. For comparisons among three or more groups, one-way ANOVA or the Kruskal–Wallis test was used, depending on distribution. Correlation analysis was performed using Pearson's or Spearman's coefficient, depending on data normality. Bivariate linear regression was used when significant positive correlations were observed.

Ethical Considerations

This study was conducted in accordance with the ethical principles for medical research involving human subjects, as outlined in the Declaration of Helsinki and Resolution 008430 of 1993 from the Colombian Ministry of Health (5,6). The study protocol was reviewed and approved by the Research Ethics Committee of Universidad Libre, Pereira branch (Colombia) and the Ethics Committee of the Universidad Internacional Iberoamericana de México (Approval Code: 2022-11-04-001). All participants provided written informed consent prior to their participation.

Results

A total of 102 participants were included, equally distributed between Group A (hybrid immunity) and Group B (vaccine-induced immunity). Most were women (80.4%), with a mean age of 43.1 years and a mean BMI of 26.4 kg/m². Comorbidities such as hypertension and diabetes were present in 15.7% and 7.8% of participants, respectively. Over 60% were classified as overweight, and nearly 19% as obese. The majority had completed the primary vaccination schedule, with 44% receiving at least one booster dose. Detailed characteristics are presented in Table 1.

The mean baseline anti-Spike IgG concentration was 1235.25 BAU/mL in Group A and 1210.19 BAU/mL in Group B, with no statistically significant difference between groups ($p = 0.830$; Table 2).

When stratified by sex, age, BMI, and comorbidities, no significant differences in antibody titers were found between groups (Table 3). Slight trends were observed—e.g., higher titers in older participants in Group A and in those with mild prior COVID-19—but none reached statistical significance.

Antibody concentrations by vaccine type showed the highest levels among Moderna and Pfizer recipients in both groups, while lower titers were seen in those who received AstraZeneca or Janssen. However, intergroup differences remained nonsignificant (Table 4).

Participants with homologous and heterologous immunization schemes had similar antibody concentrations. A moderate positive correlation was observed between the

Table 1
Baseline characteristics of study participants by group

Variable	Group A (n = 51)	Group B (n = 51)	Total (n = 102)
Sex, n (%)			
Male	10 (19.6)	10 (19.6)	20 (19.6)
Female	41 (80.4)	41 (80.4)	82 (80.4)
Age (years), mean ± SD	45.1 ± 14.8	41.2 ± 14.6	43.1 ± 2.75
Weight (kg), mean ± SD	70.53 ± 3.18	68.18 ± 13.53	69.35 ± 1.66
Height (m), mean ± SD	1.62 ± 0.08	1.61 ± 0.06	1.61 ± 0.007
BMI (kg/m²), mean ± SD	26.55 ± 5.02	26.21 ± 5.03	26.38 ± 0.24
Comorbidities, n (%)			
Hypertension (HTN)	9 (17.6)	7 (13.7)	16 (15.7)
Diabetes Mellitus (DM)	5 (9.8)	3 (5.9)	8 (7.8)
Overweight	32 (62.7)	31 (60.8)	63 (61.8)
Obesity	9 (17.6)	10 (19.6)	19 (18.6)
Habits, n (%)			
Smoking	1 (2.0)	2 (3.9)	3 (2.9)
Alcohol consumption	6 (11.8)	9 (17.6)	15 (14.7)
Socioeconomic status, n (%)			
Level 1	16 (31.4)	22 (43.1)	38 (37.3)
Level 2	13 (25.5)	16 (31.4)	29 (28.4)
Level 3	12 (23.5)	11 (21.6)	23 (22.5)
Level 4	7 (13.7)	0 (0.0)	7 (6.9)
Level 5	2 (3.9)	1 (2.0)	3 (2.9)
Level 6	1 (2.0)	1 (2.0)	2 (2.0)
Clinical severity of COVID-19			
Mild	34 (66.7)	0 (0.0)	34 (33.3)
Moderate	13 (25.5)	0 (0.0)	13 (12.7)
Severe	4 (7.8)	0 (0.0)	4 (3.9)
Vaccine received, n (%)			
Pfizer (BNT162b2)	21 (41.2)	10 (19.6)	31 (30.4)
Moderna (mRNA-1273)	8 (15.7)	9 (17.6)	17 (16.7)
AstraZeneca (ChAdOx1)	3 (5.9)	5 (9.8)	8 (7.8)
Sinovac (CoronaVac)	13 (25.5)	12 (23.5)	25 (24.5)
Janssen (Ad26.COV2.S)	6 (11.8)	6 (11.8)	12 (11.8)
Full vaccination scheme	45 (88.2)	43 (84.3)	88 (86.3)
Booster doses received, n (%)			
1 Dose	22 (43.1)	23 (45.1)	45 (44.1)
2 Doses	18 (35.3)	19 (37.3)	37 (36.3)
3 Doses	4 (7.8)	0 (0.0)	4 (3.9)
4 Doses	1 (2.0)	1 (2.0)	2 (2.0)

Table 2
Descriptive and inferential analysis of IgG anti-S concentration in Group A and B

Group	IgG anti-S (BAU/mL)Mean ± SD	95% CI	p-value*
Group A (n = 51)	1235.25 ± 585.32	1070.63 – 1399.88	0.83
Group B (n = 51)	1210.19 ± 588.55	1044.66 – 1375.73	

* Student's t-test

Table 3
IgG anti-S concentration by socio-demographic and comorbidity variables in Groups A and B

Variable		Group	n	Mean ± SD (BAU/mL)	95% CI	p-value
Sex	Male	A	10	1336.60 ± 687.40	910.20 – 1781.80	0.847#
		B	10	1394.70 ± 640.90	997.33 – 1790.67	
	Female	A	41	1210.54 ± 564.67	1037.36 – 1382.64	0.680*
		B	41	1165.20 ± 574.42	989.30 – 1340.70	
Age	> 43 years	A	27	1318.00 ± 552.46	1099.45 – 1536.55	0.107*
		B	21	1053.71 ± 552.62	802.16 – 1305.27	
	< 43 years	A	24	1142.17 ± 618.62	880.95 – 1403.39	0.271#
		B	30	1319.73 ± 597.04	1096.79 – 1542.68	
Overweight	Yes (BMI 25–29.9)	A	23	1387.43 ± 576.01	1138.35 – 1636.52	0.284#
		B	21	1212.76 ± 566.16	955.05 – 1470.47	
	No	A	19	1117.05 ± 597.42	829.10 – 1405.00	0.461#
		B	20	1258.85 ± 637.49	960.49 – 1557.21	
Obesity	Yes (BMI ≥ 30)	A	9	1095.89 ± 551.52	735.02 – 1454.98	0.965*
		B	10	1107.50 ± 580.66	747.52 – 1466.48	
	No	A	42	1265.12 ± 594.38	1085.36 – 1444.64	0.774#
		B	41	1235.24 ± 594.85	1053.18 – 1416.82	
Hypertension	Yes	A	9	1391.78 ± 510.35	1057.80 – 1724.20	0.975*
		B	6	1383.67 ± 423.76	1044.54 – 1721.46	
	No	A	42	1201.71 ± 600.39	1019.54 – 1382.46	0.905#
		B	45	1187.07 ± 607.10	1009.65 – 1364.35	
Diabetes	Yes	A	5	1092.20 ± 414.18	729.12 – 1454.88	0.936*
		B	3	1059.67 ± 766.86	192.20 – 1925.80	
	No	A	46	1250.80 ± 602.42	1071.91 – 1429.70	0.797#
		B	48	1219.60 ± 584.76	1049.81 – 1389.40	
Metabolic Syndrome	Yes	A	16	1214.31 ± 559.04	940.10 – 1487.90	0.965*
		B	16	1222.94 ± 536.17	959.36 – 1484.64	
	No	A	35	1244.83 ± 604.69	1043.90 – 1444.10	0.741#
		B	35	1204.37 ± 618.44	999.26 – 1408.74	

*Student's t-test; #Mann–Whitney U test.

Table 4
Descriptive and inferential analysis of IgG anti-S levels by vaccine type and COVID-19 history

Vaccine Type	Group	n	IgG anti-S (BAU/mL)Mean ± SD	95% CI	p-value
Pfizer (BNT162b2)	A	21	1481.38 ± 546.55	1232.59 – 1730.17	0.320#
	B	19	1284.42 ± 594.52	997.87 – 1570.97	
Moderna (mRNA-1273)	A	8	1230.13 ± 619.29	712.38 – 1747.87	0.167#
	B	9	1655.89 ± 552.75	1231.00 – 2080.78	
AstraZeneca (ChAdOx1)	A	3	641.00 ± 463.33	−509.98 – 1791.98	0.806*
	B	5	706.00 ± 270.91	369.62 – 1042.38	
Sinovac (CoronaVac)	A	13	1178.85 ± 494.04	880.30 – 1477.40	0.673*
	B	12	1094.17 ± 495.11	779.59 – 1408.74	
Janssen (Ad26.COV2.S)	A	6	800.00 ± 566.23	205.77 – 1394.23	0.648*
	B	6	958.83 ± 603.12	325.89 – 1591.78	

*Student's t-test; #Mann–Whitney U test

number of booster doses and antibody levels in Group A (Spearman's rho = 0.453, p = 0.001), but not in Group B (Table 5).

Table 5
Spearman correlation between IgG anti-S antibody levels and number of booster doses (Group A and B)

Group	Spearman's rho	p-value	Strength of correlation
up A	0.453	0.001	Moderate
up B	0.18	0.205	Very weak

Linear regression analysis in Group A indicated that each additional booster dose predicted an increase of approximately 276.6 BAU/mL in antibody levels (p = 0.002). Based on this model, a fifth booster dose could raise titers to around 2216.75 BAU/mL (Table 6).

Table 6
Simple linear regression model of antibody titers by number of booster doses (Group A)

Predictor	B (Unstandardized)	SE	β (Standardized)	t	p-value
(Constant)	833.96	146.43	—	5.7	<0.001
Number of boosters	276.57	86.54	0.415	3.2	0.002

Discussion

More than two years after the official end of the pandemic, SARS-CoV-2 remains a pathogen of high pandemic potential (7). Vaccination continues to be the most effective strategy to reduce COVID-19 morbidity, mortality, and viral transmission (8). In this context, population-level serological surveillance is essential to assess the durability of immunity, vaccine effectiveness, and the performance of immunization strategies (9).

All participants in this study exhibited elevated levels of trimeric anti-S IgG antibodies, with titers up to 11 times the reference cutoff (≥105 BAU/mL), and a 100% seropositivity rate in both groups, with no significant differences. Antibody persistence reached up to 23 months after the last booster dose, indicating a sustained humoral response. Our findings are consistent with studies conducted in Bogotá and Cali, which reported high seropositivity rates and persistent antibody responses following vaccination, regardless of prior infection status (10,11). In contrast, research from Armenia found significantly higher antibody titers among previously infected individuals (12). These discrepancies may be explained by regional, sociodemographic, or temporal differences, as earlier studies were conducted during the acute phases of the pandemic, whereas ours took place in a post-pandemic context characterized by widespread natural and vaccine-induced immunity.

Early research on hybrid immunity (HI) showed that prior infection enhanced vaccine-induced responses, resulting in higher antibody titers and improved cross-protection against viral variants (14–17). However, our study found no significant differences between groups. This may be attributed to widespread community exposure to SARS-CoV-2 after the pandemic, including among asymptomatic individuals, suggesting that subclinical infections could also contribute to immune reinforcement (18).

Lifestyle factors, including alcohol and tobacco use, and socioeconomic status also showed no significant differences in antibody titers, in contrast with findings from other settings (19-21). All subgroups demonstrated high reactivity against the spike protein.

Host-related factors such as sex, age, and comorbidities showed no significant association with anti-S IgG levels. Although previous studies have reported reduced vaccine immunogenicity in older adults and individuals with chronic conditions such as hypertension, diabetes, overweight, and obesity (22–25), this was not observed in our cohort. This may reflect a robust immune response in the study population or the effectiveness of current booster-based immunization schemes across diverse health profiles.

Regarding clinical history of COVID-19, participants who had experienced mild, moderate, or severe illness exhibited elevated anti-S IgG titers with no significant differences. This aligns with evidence suggesting that clinical severity does not necessarily correlate with humoral response magnitude due to the involvement of diverse immune mechanisms (26-28).

Among vaccine types, higher reactivity was observed with mRNA platforms (Pfizer, Moderna), followed by inactivated virus vaccines (Sinovac), and lower reactivity with viral vector vaccines (Janssen, AstraZeneca). However, no statistically significant differences were found between groups. These findings differ from those in Armenia, where prior infection appeared to modulate antibody responses depending on the vaccine received (12). Genetic background, methodological variations, and immunization schemes may underlie these discrepancies.

Both homologous and heterologous vaccination schemes proved similarly effective in inducing antibody responses, with no significant differences between groups. These results are consistent with international evidence supporting the immunogenic equivalence of both approaches (29,30).

A positive and statistically significant correlation was observed between the number of booster doses and anti-S IgG titers in previously infected individuals. This suggests that hybrid immunity may be enhanced by successive boosters, activating both innate trained immunity and adaptive memory responses.

This study has several limitations. First, the cross-sectional design prevents the establishment of causal relationships or the assessment of longitudinal antibody

kinetics. Second, the reliance on self-reported data for infection history and vaccination details may introduce recall bias. Additionally, neutralizing antibody activity was not assessed, limiting functional interpretation of the humoral response.

Conclusion

This study demonstrated high and sustained anti-S IgG seropositivity in a Colombian adult population, regardless of prior infection history. No significant differences were observed based on sex, age, comorbidities, or vaccine type, suggesting a broadly effective immune response in the post-pandemic context. The results support the ongoing use of booster doses and highlight the importance of continued serological monitoring to guide immunization strategies. Further studies are needed to explore functional immunity and the role of hybrid exposure in shaping long-term protection.

Authors' contributions

Torres J. Franklin E.: Conceptualization, Methodology, Project administration, Investigation. **Mendoza T. Evelyn**: Literature review, Data visualization, Writing - Original Draft Preparation. **Alcocer O. Adalgisa**: Formal analysis, Writing - Original Draft Preparation. **Torres F. María F.**: Investigation, Data curation, Writing - Original Draft Preparation. **Mendoza Z. Daniel**: Investigation, Data curation, Writing - Original Draft Preparation. **Cantillo B. Mariangel**: Investigation, Data curation, Writing - Original Draft Preparation. **Echeverría B. David**: Investigation, Methodology, Data visualization, Writing - Original Draft Preparation. **Varón T. Valentina**: Investigation, Methodology, Data visualization, Writing - Original Draft Preparation. **Pineda A. Giselle**: Investigation, Methodology, Data visualization, Writing - Original Draft Preparation.

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Conflict of interest

The authors declare no conflicts of interest.

Availability of data

The datasets generated and /or analyzed during current study available from the corresponding author on reasonable request.

Ethical statement

The authors declare that the present study was conducted under the strictest ethical conditions.

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